Differential regulation of mouse and human nephron progenitors by the Six family of transcriptional regulators.

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Public Summary:
Mammalian nephrons are derived from a distinct population of self-renewing and multi-potent nephron progenitor cells (NPC) during embryonic development. Two related transcription factors Six1 and Six2 play critical but different roles in NPC. Six1 is transiently activated to initiate nephrogenesis, while enduring Six2 expression maintains self-renewal of NPC throughout the entire process which ends early postnatal. Comparative to mouse, SIX2 is also expressed in a specific domain within the human kidney nephrogenic zone, but the SIX2-dependent transcriptional regulation of human nephron development has never been examined before. Here we compared the genome-wide regulatory actions of Six2/SIX2 in mouse and human NPC by chromatin immunoprecipitation followed by DNA sequencing (ChIP-seq). Surprisingly, SIX1 was identified as a regulatory target of SIX2 unique to human. Expression of SIX1 in human but not mouse NPC was validated by both RNA-Sequencing and immunostaining. The putative Six1/SIX1 enhancer are conserved between mouse and human, but presence of Six2 is detected only in the human counterpart, which correlates with locally active chromatin in human and repressive chromatin in mouse. When the human SIX1 enhancer was introduced into mouse, its activity is transient and mimics the pre-nephrogenic pattern of Six1. Taken together, our data suggests differential regulation of SIX factors between mouse and human, likely contributing to the inter-species differences in kidney development.

Scientific Abstract:
Nephron endowment is determined by the self-renewal and induction of a nephron progenitor pool established at the onset of kidney development. In the mouse, the related transcriptional regulators Six1 and Six2 play non-overlapping roles in nephron progenitors. Transient Six1 activity prefigures, and is essential for, active nephrogenesis. By contrast, Six2 maintains later progenitor self-renewal from the onset of nephrogenesis. We compared the regulatory actions of Six2 in mouse and human nephron progenitors by chromatin immunoprecipitation followed by DNA sequencing (ChIP-seq). Surprisingly, SIX1 was identified as a SIX2 target unique to the human nephron progenitors. Furthermore, RNA-seq and immunostaining revealed overlapping SIX1 and SIX2 activity in 16 week human fetal nephron progenitors. Comparative bioinformatic analysis of human SIX1 and SIX2 ChIP-seq showed each factor targeted a similar set of cis-regulatory modules binding an identical target recognition motif. In contrast to the mouse where Six2 binds its own enhancers but does not interact with DNA around Six1, both human SIX1 and SIX2 bind homologous SIX2 enhancers and putative enhancers positioned around SIX1. Transgenic analysis of a putative human SIX1 enhancer in the mouse revealed a transient, mouse-like, pre-nephrogenic, Six1 regulatory pattern. Together, these data demonstrate a divergence in SIX-factor regulation between mouse and human nephron progenitors. In the human, an auto/cross-regulatory loop drives continued SIX1 and SIX2 expression during active nephrogenesis. By contrast, the mouse establishes only an auto-regulatory Six2 loop. These data suggest differential SIX-factor regulation might have contributed to species differences in nephron progenitor programs such as the duration of nephrogenesis and the final nephron count.